Technology Assessment Program
Office of Patient Care Services

Bibliography*: Treatments for Metastatic Castrate-Resistant Prostate Cancer

*Selected, quality filtered, not subject to external review

POLICY ISSUES: The National Program Director for Oncology requested assistance from the VHA Office of Patient Care Services (OPCS) in determining the effectiveness and provision of newly FDA-approved sipuleucel-T (PROVENGE®, Dendreon Corporation) for treatment of asymptomatic or minimally symptomatic metastatic castrate-resistant prostate cancer (CRPC).

The VA Technology Assessment Program (VATAP) was charged with gathering the best available evidence from research to support deliberations of a Clinical Expert Panel assembled as part of VA's National Medical Technology Assessment Protocol (NMTAP). The NMTAP provides unbiased, evidence-based advice and recommendations for clinical use of new technologies in VA. The essential role of the Clinical Expert Panel in this process was to provide guidance for use of sipuleucel-T in VA based on the best available evidence, clinical expertise and judgment.

Of particular interest to VA were the following issues:

1. **What is the effectiveness of sipuleucel-T relative to other available treatments for treatment of CRPC?**

2. In the first year of approval, availability of sipuleucel-T will be limited to approximately 2000 patients across 50 centers that were original FDA-approved clinical trial sites.[1] However, none are VA facilities. While Dendreon Corp. intends to increase manufacturing capacity over time, there are potential significant implications for the provision of this treatment option to Veterans: *"One non-VA facility indicated that patients from other facilities (e.g., VAs) would be at the bottom of priority list and they would probably be using a lottery to select among patients already being seen at their facility."* (Michael Kelly: email communication, May 25, 2010) **How will VA provide its patients access to sipuleucel-T?**

3. The cost of treatment including contracted leukapheresis[2] is estimated to be $93,000 ($31,000 per treatment for three treatments).[3] **If the manufacturer allows, could VA achieve higher efficiency and less patient care fragmentation by providing leukapheresis on site, or will this only be available by fee basis or contract?**

BACKGROUND: Prostate cancer is the most frequently diagnosed cancer and the second most common cause of cancer in men.[4] In 2010, an estimated 217,730 new cases of prostate cancer will be diagnosed with, and an estimated 32,050 will die from, prostate cancer in the United States. During 2002-2006, the median age at diagnosis was 68 years.

In VA, cancer of the prostate gland is the most commonly diagnosed tumor. In FY2009 there were an estimated 146,214 total cases of prostate cancer, representing 27.3% of total cases of cancer, and an estimated 2,224 new cases were diagnosed.[5] VA recognizes a positive association between prostate cancer and exposure to Agent Orange and other herbicides used

[1] http://www.provenge.com/pdf/Dendreon-Approval-Press-Release.pdf accessed June 2, 2010.
[2] Leukapheresis is a laboratory process that removes white blood cells (leukocytes) from the blood of the donor.
[3] http://www.fiercebiotech.com/story/dendreon-provenge-cost-93k-full-course-treatment/2010-04-29 accessed June 2, 2010.
[4] http://www.cancer.org/downloads/STT/Cancer_Facts_and_Figures_2010.pdf accessed June 14, 2010.
[5] VA Central Cancer Registry Cumulative Data Summary Reports for 2008 and 2009 (note: incomplete reporting of data for FY2008 and FY2009). http://vaww.medicalsurgical.va.gov/cancer/VACCR_Cumulative_Data.asp , accessed June 9, 2010.

during military service.[6] Therefore, Veterans, particularly those who served in Vietnam, are at higher risk for prostate cancer given the probability of this exposure and their age.

Notably, while prostate cancer is the second leading cause of cancer death in men, the overall 5-year relative survival approaches 100% for those with localized or regionalized disease, in part due to earlier diagnosis and improvements in treatment. Despite these advances, an estimated 20-40% will have disease progression requiring androgen deprivation therapies involving surgical (orchiectomy) or medical castration. In most of these individuals the disease will progress to distant sites despite low serum androgen levels.[7] This stage is defined as castrate-resistant prostate cancer (CRPC).

Currently available treatments[8]

A wide range of current and emerging treatment strategies exist to treat CRPC. Many CRPCs are both biologically and clinically heterogeneous and may still respond to some androgen-targeting therapies, thus widening the range of potentially effective therapies. Other alternative therapies include, but are not limited to, antiangiogenic agents, cytotoxic agents, and immunotherapy using vaccination agents. Mitoxantrone, estramustine and docetaxel are FDA-approved for use as first-line chemotherapy in CRPC with several agents under evaluation in Phase III trials. Thus far, docetaxel in combination with prednisone is the only agent to have shown a survival benefit (median 2.4 months). Docetaxel-based chemotherapy is now regarded as the standard of care.[9,10,11]

Alternative therapies that have not demonstrated improvement in survival may have a role in slowing disease progression, palliation and improved quality of life. The challenge for a clinician is to identify which CRPCs will respond to a particular therapeutic regimen.

If cancer progresses through first-line options, there are promising alternatives, including mitoxantrone and docetaxel if not used as first-line options.[12] One alternative is the newly FDA-approved agent, sipuleucel-T, based on results from Phase III trials. Another agent for which Phase III trial results were reported is satraplatin. However, the manufacturer of satraplatin, GPC Biotech, withdrew its FDA New Drug Application because the trial did not achieve the desired endpoint of overall survival.

Sipuleucel-T

While the precise mechanism of action is unknown, sipuleucel-T is an autologous cellular immunotherapy designed to stimulate a patient's own immune response against prostate cancer. In this respect, it performs similarly to a vaccine and is often referred to as a "vaccine-based" immunotherapy. However, sipuleucel-T requires leukapheresis to isolate a patient's peripheral mononuclear cells. These cells are activated (or "vaccinated") *ex vivo* with a

[6] http://www.publichealth.va.gov/exposures/agentorange/treatment.asp, accessed June 9, 2010.
[7] Ward JF, Moul JW. Rising prostate-specific antigen after primary prostate cancer therapy. Nature Clinical Practice Urology 2005 Apr;2(4):174-82.
[8] http://www.cancer.gov/cancertopics/pdq/treatment/prostate/HealthProfessional/page10/print
[9] Basch Ethan, M., et al., *American Society of Clinical Oncology endorsement of the Cancer Care Ontario Practice Guideline on nonhormonal therapy for men with metastatic hormone-refractory (castration-resistant) prostate cancer*. Journal of clinical oncology - official journal of the American Society of Clinical Oncology, 2007. **25**(33): p. 5313-8.
[10] National Collaborating Center for Cancer, *Prostate cancer diagnosis and treatment*. 2008, NICE. National Institute for Clinical Excellence: London. p. 38. http://guidance.nice.org.uk/CG58
[11] Winquist, E., et al., *Non-hormonal systemic therapy in men with metastatic hormone-refractory prostate cancer: a clinical practice guideline* 2005, Program in Evidence Based Care PEBC. Genitourinary Cancer Disease Site Group,: Hamilton p. 4. http://www.cancercare.on.ca/pdf/pebc3-15s.pdf
[12] Vishnu et al. OncoTargets and Therapy 2010;3:39-51.

recombinant human protein (PAP-GM-GAF) containing prostatic acid phosphatase (PAP), which is an antigen expressed in prostate cancer cells, that is linked to granulocyte-machrophage colony-stimulating factor. These activated immune cells are then returned to the patient to target and treat the prostate cancer.

Regulation[13]

FDA approved sipuleucel-T on April 29, 2010 for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. Approval was based on the following efficacy data from one Phase III study (D9902B; also known as the IMPACT trial (Immunotherapy for Prostate Adenocarcinoma Treatment)) with support from two other similar trials (D9901 and D9902A). Details from each published study are abstracted in Table 1.

D9901 and D9902A were identically designed contemporaneous studies. Each used time-to-objective-disease-progression as the primary endpoint, the results of which were integrated in an analysis of safety and efficacy. Enrollment in D9902A was stopped based on initial disease progression results in D9901 and before the availability of survival results. Study D9902A was then amended to become D9902B.

Eligibility criteria included metastatic disease in the soft tissue and/or bone with evidence of progression either at these sites or by serial Prostate Specific Antigen (PSA) measurements. Exclusion criteria included visceral (liver, lung, or brain) metastases, moderate to severe prostate cancer-related pain, and use of narcotics for cancer-related pain. Eligibility criteria and characteristics of subjects who received sipuleucel-T are detailed in Table 1.

Table 1. Characteristics of subjects in Phase III studies of sipuleucel-T
Sources: FDA Summary Basis for Regulatory Action STN# 125197 and individually published reports[14,15,16] *as noted in the table*

Study characteristics	D9901 (Small 2006)	D9902A (Higano 2009)	D9902B (Kantoff 2010)
Eligibility criteria	• Histologically confirmed adenocarcinoma of the prostate • Radiologic evidence of metastases or by PSA Consensus criteria • Asymptomatic or minimally symptomatic • Serum testosterone levels < 50 ng/dL • Expected survival ≥ 16 weeks (≥ 3 months in D9902A) • ECOG performance status of 0 or 1 • Any Gleason score • Positive immunohistochemistry staining for PAP in ≥ 25% of cells assessed at a central laboratory • Negative serologic tests for HIV, human T-cell leukemia virus type 1, hepatitis B, hepatitis CAdequate hematologic, renal and hepatic function: • WBC at least 2,000/mm3, Absolute neutrophil count at least 1,000/mm3, Platelet count at least 100,000/mm3,		

[13] *Source: FDA Summary Basis for Regulatory Action STN# 125197* http://www.fda.gov/downloads/BiologicsBloodVaccines/CellularGeneTherapyProducts/ApprovedProducts/UCM213114.pdf accessed May 28, 2010.

[14] Small EJ, Schellhammer PF, Higano CS, Redfern C, Nemunaitis JJ, Valone FH, et al. Placebo-controlled phase III trial of immunologic therapy with sipuleucel-T (APC8015) in patients with metastatic, asymptomatic hormone refractory prostate cancer. *Journal of Clinical Oncology,* 2006; 24(19): 3089-3094.

[15] Higano CS, Schellhammer PF, Small EJ, Burch PA, Nemunaitis J, Yuh L, et al. Integrated data from 2 randomized, double-blind, placebo-controlled, phase 3 trials of active cellular immunotherapy with sipuleucel-T in advanced prostate cancer. *Cancer,* 2009; 115(16): 3670-3679.

[16] Kantoff P, Higano C, Shore N, Berger ER, Small EJ, Penson DF, et al. Sipuleucel-T Immunotherapy for Castration-Resistant Prostate Cancer. *New England Journal of Medicine,* 2010; 363(5): 411-423.

Study characteristics	D9901 (Small 2006)	D9902A (Higano 2009)	D9902B (Kantoff 2010)
	Hemoglobin at least 9.0 g/dL • Bilirubin no greater than 2 times upper limit of normal (ULN) ALT and AST no greater than 5 times ULN • Creatinine no greater than 2.0 mg/dL • Prior investigational agents, other hormones, Saw Palmetto, PC-SPES, or other herbal preparations were allowed provided they were discontinued at least 1 month before treatment. • No prior biologic therapy • Concurrent bisphosphonate therapy was permitted provided therapy was initiated at least 30 days before registration and was not discontinued (or initiated) during the study • Prior radiation therapy completed ≥ 1 month before treatment • Radiopharmaceuticals not administered within 1 year of treatment. • Patients without prior bilateral orchiectomy continued on gonadal suppression with a luteinizing hormone-releasing hormone agonist throughout the trial. • No more than 1 prior chemotherapy regimen • Prior chemotherapy permitted if given at least 6 months before, or at least 3 months had elapsed and the CD4_T-cell count was > 400		
Exclusion criteria	• Patients who required concurrent systemic corticosteroids or those who received prior immunotherapy • Patients with moderate to severe prostate cancer-related bone pain, or the requirement of opioid analgesics for cancer pain • Patients with visceral metastases • D9902B also stated excluding patients with pathologic long bone fractures, spinal cord compression • D9902B also stated excluding patients who completed treatment less than one month prior with systemic glucocorticoids, surgery or systemic therapy for prostate cancer other than medical or surgical castration		

Characteristics of treatment group	• Median age: 73, range 47-85
	• 89% white
	• Bisphosphonate use at entry: 3.7%
	• Mets:
	  ○ bone only 42.7%
	  ○ soft tissue only 6.1%
	  ○ bone and soft tissue 51.2%
	• Number of bone mets: > 10=40.2%
	• ECOG score: 0=75.6%
	• Median Gleason score: 7; 61% ≤ 7
	• Prior chemotherapy: 3.7%
	• Received docetaxel-based chemotherapy after study treatment: 35.9%
	• Median PSA (ng/mL): 46.0, range 3.5-3621
	• Median PAP (ng/mL): 7.0, range 0.7-250.5
	• Median alk phos (U/L): 102.0, range 42.0-1233.0)
	• Median HGB (g/dL): 13.0, range 8.5-16.5
	• Median LDH (U/L): 173.5, range 119-533
		• Median age: 70, range 51-84
		• 91% white
		• Bisphosphonate use at entry: 3.7%
		• Mets:
		  ○ bone only 47.7%
		  ○ soft tissue only 10.8%
		  ○ bone and soft tissue 41.5%
		• Number of bone mets: > 10=50.8%
		• ECOG score: 0=78.5%
		• Median Gleason score: 68.7% ≤ 7
		• Prior chemotherapy: 11.1%
		• Received any chemotherapy after study treatment: 57% (Integrated study data)
		• Received docetaxel-based chemotherapy after study treatment: 35% (Integrated study data)
		• Median PSA (ng/mL): 61.3, range 8.0 -936.5
		• Median PAP (ng/mL): 4.5, range 0.7-230.0
		• Median alk phos (U/L): 140.0, range 50.0-3900.0)
		• Median HGB (g/dL): 12.8, range 9.2-15.8
		• Median LDH (U/L): 187.0, range 101-1730
			• Median age: 72, range 49-91
			• 89% white
			• Bisphosphonate use: 48%
			• Mets:
			  ○ bone only 50.7%
			  ○ soft tissue only 7%
			  ○ bone and soft tissue 41.9%
			• Number of bone mets: ≥ 10 = 43%
			• ECOG score: 0=82%
			• Gleason scores ≥ 4=57.8%
			• Prior therapy:
			  ○ Chemotherapy: 19.6%
			  ○ Docetaxel: 15.5%
			  ○ Androgen deprivation: 100%
			  ○ Combined androgen blockade: 82%
			  ○ Med/Surgical castration alone: 18.2%
			  ○ Orchiectomy: 9.4%
			  ○ Radical prostatectomy: 35.5%
			  ○ Local radiotherapy 54.3%,
			• Baseline pain score: 0=51.5%
			• All had baseline testosterone levels < 50 ng/mL
			• Median PSA (ng/mL): 51.7
			• Median PAP (ng/mL): 2.7
			• Median alk phos (U/L): 99
			• Median HGB (g/dL): 12.9
			• Median LDH (U/L): 194
			• Median white cell count (cells/mm^3): 6200
			• Median total absolute neutrophil count (cells/mm^3): 4000

D9902B used overall survival as the primary endpoint and was analyzed independently from D9902A. In Study D9902B 19.6% of subjects had received prior chemotherapy, including 15.5% receiving docetaxel, and 7% more subjects in the treatment arm received docetaxel following study treatment, compared to the placebo arm. In Study D9901 12% more subjects in the placebo arm received docetaxel following disease progression compared to the treatment arm. Subsequent treatment with docetaxel did not affect overall survival rates in Studies D9902B and D9901.

Table 2. Summary of Overall Survival Analysis Results for Sipuleucel-T
Source: FDA Summary Basis for Regulatory Action STN# 125197

NCI Study ID	Sipuleucel-T Median survival	Placebo Median survival	Sipuleucel-T vs. placebo Hazard Ratio for Death (95% CI)	p-value
D9902B (N=512) NCT00065442	25.8 (N=341)	21.7 (N=171)	0.775 (0.614, 0.979)	0.032
D9901 (N=127) NCT00005947	25.9 (N=82)	21.4 (N=45)	0.586 (0.388, 0.884)	0.010
D9902A (N=98) NCT01133704	19.0 (N=65)	15.7 (N=33)	0.786 (0.484, 1.278)	0.331
Integrated Studies (N=737)	25.4 (N=488)	21.5 (N=249)	0.734 (0.612, 0.881)	0.0009

The safety results from all three trials were integrated, analyzed and presented in Table 3. The safety review was based on safety data from the three Phase III trials listed above and one additional Phase III study (NCT00779402). The population consisted of 904 subjects (601 treatment; 303 control) who underwent at least one leukapheresis procedure.

Table 3. FDA Safety Review Data
Source: FDA Summary Basis for Regulatory Action STN# 125197

Adverse event (AE)	% treatment subjects
Any AE	98.3%
Mild or moderate severity	67.4%
Severe (Grade 3)	23.6%
Life-threatening (Grade 4)	4.0%
Fatal (Grade 5)	3.3%
Cerebrovascular event	3.5% (vs. 2.6% in controls) *Incidence rates (IR) reported as # events/ 100 patient-years (95% CI) of follow-up: Higano (2009) sipuleucel-T IR = 3.99 (1.99-7.14) vs. placebo IR 1.58 (0.19-5.69) Kantoff (2010) sipuleucel-T IR = 1.33 (0.58-2.62) vs. placebo IR 1.11 (0.23-3.24)
Other findings	
Most common AE occurring in Grade 3-5 (≥ 2%)	Back pain, chills
Most common occurring in ≥ 15% of any severity	Chills, fatigue, fever, back pain, nausea, arthralgia and headache
AE most likely related to study procedures (i.e. leukapheresis or infusion) that occurred in both treatment and control groups	
Citrate toxicity	14-15% in each groups
Paresthesia	"common" to each group

FDA concluded the following:

- *"No difference between the two study arms in time to objective disease progression, progression free survival, time to clinical progression, or time to prostate-specific antigen (PSA) doubling time was observed in any of the Phase 3 studies. The reason for the dissociation between overall survival and these other outcome measures is unclear. However, overall survival is the most reliably measured and clinically meaningful of these endpoints."*

- *"Treatment with sipuleucel-T was associated with a statistically significant improvement in overall survival, compared to a placebo control. Median survival was 4.1 months longer in subjects who received sipuleucel-T than in subjects who received placebo. The finding was supported by multiple sensitivity and subgroup analyses."*

- In a subset of subjects, some specific immune responses were noted post-sipuleucel-T treatment, but the clinical meaningfulness of these responses is unclear.

- As FDA will generally rely on results from a single trial only when a second trial is not ethical and/or feasible, in this case where a significant survival advantage was found in D9902B: *"D9902B, supported by the results of D9901 and D9902A, meets the regulatory standard for a single trial that provides the substantial evidence of effectiveness necessary to support a marketing approval."*

- Results for the risk of any cerebrovascular event associated with sipuleucel-T were conflicting. Because of the potential for a slightly increased risk of a cerebrovascular event with sipuleucel-T, FDA requires that such safety information be included in package labeling, and that Dendreon be required to conduct a postmarketing registry study enrolling 1,500 patients with prostate cancer who receive sipuleucel-T and report the findings by September 30, 2016.

- The recommended course of therapy for sipuleucel-T is three complete doses, given at approximately 2-week intervals. This therapeutic course is based on safety data from four randomized, placebo-controlled studies using this time interval. However, the maximum dosing interval has not been established.

Reimbursement

Given quite recent FDA approval, the manufacturer is in the early stages of providing a limited quantity of sipuleucel-T and no reimbursement information is available. The Centers for Medicare and Medicaid Services opened a National Coverage Analysis of autologous cellular immunotherapy treatment of prostate cancer on June 30, 2010 with a decision expected in 2011.[17]

METHODS: TAP approached the review by focusing on available systematic reviews, health technology assessments (HTA) and meta-analyses of second-line treatment for metastatic CRPC, and supplementing them with updated information. Then, TAP queried members of the

[17] http://www.cms.gov/mcd/viewtrackingsheet.asp?from2=viewtrackingsheet.asp&id=247& accessed July 2, 2010.

International Network of Agencies for Health Technology Assessment (INAHTA; www.inahta.org) electronically via their listserv on May 28, 2010 for existing systematic reviews, HTAs or meta-analyses or reports in process on treatments for metastatic CRPC.

Searches

On May 28, 2010 and again on June 17, 2010 TAP carried out extensive searches of PubMed, EMBASE, MEDLINE, Current Contents, the Cochrane Library and clinical guidelines.gov using terms: advanced prostate cancer, castration resistant, or metastatic prostate cancer therapies. Terms describing treatment resistance and drug or radio-therapies, immunotherapies, vaccines, and the specific names of the newest therapies, sipuleucel-T and PROVENGE®, were used.

Inclusion criteria

Criteria for inclusion of studies in this review were:

- The most recent systematic reviews, meta-analyses or health technology assessments (HTA) of second-line treatments for CRPC (to eliminate redundancy with earlier publications);
- Phase III primary studies of second-line treatments for CRPC that are not included in the above systematic reviews or HTAs.

Articles not published in English were excluded from review. One reviewer (Adams) selected citations for full-text retrieval, reviewed all articles, abstracted information, and prepared this review.

RESULTS: The searches retrieved 227 citations, of which 20 were retrieved as possibly relevant articles to the review based on title and abstract information. Two articles met inclusion criteria and are listed in Table 4; abstracts of these articles are presented in the End References.

Responses to the electronic INAHTA query did not identify any additional literature. Retrieved articles that were excluded from this review are listed in Table 7 in the End References along with reasons for exclusion.

TAP identified no new studies of sipuleucel-T beyond those submitted for FDA approval. TAP identified two studies, one horizon scanning report (NHSC 2009) and a scientific meeting abstract (Sartor 2010), that addressed another potential second-line treatment for metastatic CRPC—cabazitaxel (Jevtana Injection, Sanofi Aventis). Results from a multinational Phase III study of cabazitaxel in patients previously treated with a docetaxel regimen were presented at the American Society of Clinical Oncology 2010 Genitourinary Cancers meeting. The results showed a median survival advantage in the cabazitaxel group of 15.1 months compared with 12.7 months in the mitoxantrone group (HR 0.70; 95% CI 0.59, 0.83; $p < 0.0001$). The most frequent grade 3/4 toxicity was neutropenia observed in 81.7% of patients treated with cabazitaxel and 58.0% treated with mitoxantrone; rates of febrile neutropenia were 7.5% and 1.3%, respectively.

[UPDATE: On June 17, 2010, the U.S. Food and Drug Administration (FDA) approved cabazitaxel for use in combination with prednisone for treatment of patients with metastatic CRPC previously treated with a docetaxel-containing regimen. [18]]

[18] http://www.fda.gov/AboutFDA/CentersOffices/CDER/ucm216214.htm accessed July 13, 2010.

[UPDATE: On July 29, 2010 results of Study D9902B were published. See Kantoff (2010) in Table 1.]

Table 4. Summary of included articles

Citation	Topic	Report type
NHSC 2009	Cabazitaxel (XRP-6258) for metastatic CRPC—second line after docetaxel	Horizon scanning summary
Sartor 2010	Cabazitaxel or mitoxantrone with prednisone in patients with metastatic CRPC previously treated with docetaxel	Meeting abstract

CONCLUSIONS/DISCUSSION: At present there is no cure for metastatic CRPC, and until recently, treatment options were largely palliative. Trial results, which showed that docetaxel/prednisone offers a median survival advantage of an additional 2.4 months as well as palliation of symptoms and quality of life improvement over best standards of care, have given men with metastatic CRPC a new therapeutic option using docetaxel as the standard of care. Identifying additional first-line and second-line therapies that will, first, increase overall survival, and, second, improve quality of life is an active area of investigation. These options include new docetaxel-combination first-line therapies, other new first-line agents, and new post-docetaxel second-line therapies.

Both sipuleucel-T and cabazitaxel have been FDA approved. In the case of sipuleucel-T, FDA approved its use for the treatment of asymptomatic or minimally symptomatic metastatic CRPC. However, sipuleucel-T was administered before chemotherapy, including docetaxel, in a majority of patients. Cabazitaxel has been studied and approved for use in patients with metastatic CRPC previously treated with docetaxel regimens.

Sipuleucel-T resulted in a median survival advantage of 4.1 months with a 3-year survival rate of 31.7% compared with 23.0% receiving placebo. Survival was improved for patients who had an antibody titre of more than 400 against PA2024 or prostatic acid phosphotase (PAP) at any time after baseline (P<0.001), but not for those who had T-cell proliferation responses to PA2024 or PAP measured at week 6. However, sipuleucel-T offered no evidence of a measurable antitumor effect.

The limited clinical trial results for cabazitaxel show that it offers a median survival advantage of 15.1 months compared with 12.7 months with mitoxantrone (Hazard Rate 0.70; 95% CI 0.59, 0.83; $p < 0.0001$). While both agents show a modest risk-benefit profile, new therapies are needed that confer a greater survival advantage.

For now, access to sipuleucel-T will be limited to a subset of the Phase III trial sites, none of which are VA sites. Manufacturing capacity is expected to increase over time. In the future, VA will need to consider both in-house and fee basis leukapheresis capability, organizational and logistical support and their associated costs when providing Veterans with the best access to this option. Sanofi-Aventis is expected to begin marketing cabazitaxel at the end of June 2010.

Information regarding treatment costs for sipuleucel-T is provided by the manufacturer in addition to the costs of ongoing supportive care by health care providers. Payers will need to

address coverage for this treatment in light of the limited treatment options available to men with metastatic CRPC and in identifying the optimal candidates for whom such treatment would most benefit.

Several new agents are being evaluated Phase III trials listed in Table 5. Access to many novel therapies through clinical trials should be encouraged.

ONGOING RESEARCH:

Table 5. Active Phase III Trials in Second-line Therapy for CRPC
Searches carried out June 15, 2010 on www.clinicaltrials.gov for Phase III Interventional Studies with the terms "resistant", "androgen-independent" and "prostate cancer" limited to studies with a primary endpoint of "Overall Survival"

Study identifier	Intervention	Sponsor	Start date	Status
NCT00638690	Abiraterone acetate + prednisone	Cougar Biotechnology, Inc.	April 2008	Active, not recruiting
NCT00676650	Sunitinib + prednisone	Pfizer	July 2008	Recruiting
NCT00861614	Ipilimumab	Bristol-Myers Squibb	May 2009	Recruiting
NCT00974311	MDV3100	Medivation, Inc.	Not Reported	Recruiting

Small (2006) postulated that an immunotherapeutic approach such as sipuleucel-T may have gradual antitumor effects that would be more apparent in patients with less aggressive disease. Dendreon has sponsored a Phase III clinical trial (NCT00779402) of sipuleucel-T in men with early stage, non-metastatic hormone sensitive prostate cancer (see Table 6 below). To date, no results have been published.

Table 6. Active Trials of Sipuleucel-T
Searches carried out on July 28, 2010 on www.clinicaltrials.gov using search terms "sipuleucel OR provenge"

Study identifier	Title	Phase	Sponsor	Start date	Status/Proposed completion date
NCT00779402	Sipuleucel-T in early stage, non-metastatic prostate cancer	III	Dendreon	Sept 2001	Active, not recruiting
NCT00901342	Open Label Study to evaluate the safety of and magnitude of the immune responses to treatment with sipuleucel-T	II	Dendreon	Aug 2009	Active, not recruiting
NCT00715104	Sipuleucel-T as Neoadjuvant Treatment in Localized Prostate Cancer (NeoACT)	II	Dendreon	July 2008	Active/Dec 2011
NCT00715078	To Evaluate Sipuleucel-T Manufactured With Different Concentrations of PA2024 Antigen (ProACT)	II	Dendreon	Aug 2008	Active/Dec 2010
NCT00005947 (D9901)	Provenge for Asymptomatic Metastatic Hormone-Refractory Prostate Cancer	III	Dendreon	Nov 1999	Active, not recruiting

END REFERENCES

Included studies

Sartor AO, Oudard S, Ozguroglu M. Cabazitaxel or mitoxantrone with prednisone in patients with metastatic castration-resistant prostate cancer (mCRPC) previously treated with docetaxel: final results of a multinational phase III trial (TROPIC) [abstract no. 9]. In: ASCO Genitourinary Cancers Symposium, San Francisco, Mar 5-7, 2010.
http://www.asco.org/ASCOv2/Meetings/Abstracts?&vmview=abst_detail_view&confID=73&abstractID=30560

Background: Treatment of mCRPC after progression on docetaxel is an unmet medical need. Cabazitaxel (Cbz) is a novel taxane active in docetaxel-resistant tumor cell lines. TROPIC was designed to evaluate the efficacy and safety of Cbz in men with mCRPC previously treated with docetaxel. **Methods:** Men with mCRPC, ECOG PS 0-2, and adequate organ function progressing during or after docetaxel (cumulative dose ≥ 225 mg/m^2) were randomized to receive 10 mg/day of prednisone with either 3-weekly mitoxantrone 12 mg/m^2 (MP)or Cbz 25 mg/m^2 (CbzP). The primary endpoint was overall survival (OS); secondary endpoints included progression- free survival (PFS), response rate, pain measures, and safety. The study had 90% power to detect a 25% reduction in the hazard rate for death in the CbzP group (two-sided α = 0.05) after 511 events occurred. **Results:** From January 2007 to October 2008, 755 men (median age 68 yr; 84% white) were randomized 1:1 at 132 centers in 26 countries. Patients' characteristics were well balanced. Median follow-up was 12.8 months. Median number of treatment cycles was 6 for CbzP and 4 for MP. In the primary analysis based on the ITT population, patients receiving CbzP demonstrated a statistically significantly longer OS compared to MP (hazard ratio 0.70; 95%CI, 0.59, 0.83; p < 0.0001). The median survival in the CbzP group was 15.1 months compared to 12.7 months in the MP group. PFS (composite of tumor, PSA, or pain progression; or death) and response rates for tumor assessments by RECIST, PSA response, and PSA progression were also statistically significantly in favor of CbzP. The most frequent grade 3/4 toxicity was neutropenia observed in 81.7% of patients treated with CbzP and 58.0% treated with MP; rates of febrile neutropenia were 7.5% and 1.3%, respectively. **Conclusions:** Compared to MP, CbzP conferred a statistically significantly longer overall survival in patients with mCRPC progressing after treatment with a docetaxel-containing regimen.

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Excluded studies

Table 7. Excluded studies

Citation	Reason for exclusion
Antonarakis 2010	Not systematic review
Armstrong 2009	Not topic of review
Basch 2007*	Guideline
Collins 2007	Not second line therapy
Di Lorenzo 2010	Not systematic review
Garmey 2008	Not systematic review
Harzstark 2010	Not systematic review
Higano 2009*	FDA data
Lassi 2010	Not systematic review
Mulders 2009	Not topic of review
National Collaborating Center for Cancer 2008	Guideline
Regan 2010	Not Phase III
Ross 2007	Not systematic review
Scher 2008	Not topic of review
Small 2006*	FDA data
Vishnu 2010*	Not systematic review
Winquist 2005*	Guideline
Yuen 2006	Not second line therapy

* Used in background section

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Elizabeth Adams Health System Specialist Boston	Primary author	Conception and conduct of review: • Communication with client; • Clinical search strategy; • Interim information; • Analytic framework; • Draft review; • Final review.
Elaine Alligood Information Specialist Boston	Literature database searches	Database searches: • Design/conduct technical strategy; • Choose/manage databases; • Strategy text and references for report. • TAP library/archive.
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